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Synthesis and Mosquito Repellent Properties of 2,2-Dialkyl- and 2-Alkyl-4,4-dimethyl-*N*-acetyloxazolidines*

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Abstract: Nineteen novel *N*-acetyl-2,2-dialkyloxazolidines (**2**) and *N*-acetyl-2-alkyl-4,4-dimethyloxazolidines (**3**) were synthesized from commercially available carbonyl compounds and ethanolamine or 2-amino-2-methyl-1-propanol. Their bioactivity against laboratory-reared mosquitoes was compared in patch tests to known *N*-acetyl-2-alkyloxazolidines (**1**) and *N*,*N*-diethyl-*m*-toluamide (deet insect repellent). Isomeric composition measurements by [^{13}C]NMR spectroscopy favoured the *Z* rotational isomer for samples of **2** (91–96% *Z*) and the *E* rotational isomer for samples of **3** (66–71% *E*), in agreement with molecular mechanics calculations on rotational isomers of model oxazolidines. Samples of **1** were previously shown to exist in solution mostly as the *Z* isomer (60–70% *Z*). Within the optimal molecular weight range for these experimental chemicals, the duration of repellency against *Aedes aegypti* (L.), *Anopheles quadrimaculatus* Say and *Anopheles albimanus* Wiedemann generally followed the order: **1** > **2** > deet > **3**. Bioassay data are discussed in relation to the equilibrium populations of rotational isomers for substituted *N*-acetyloxazolidines.

Key words: mosquito repellents, *N*-acetyloxazolidines, rotational isomers, NMR spectroscopy, molecular mechanics.

1 INTRODUCTION

In 1991,[1] we reported the synthesis and mosquito repellent properties of a homologous series of *N*-acetyl-2-alkyloxazolidines (Fig. 1, **1**). This paper describes the synthesis of novel *N*-acetyl-2,2-dialkyloxazolidines (**2**) and *N*-acetyl-2-alkyl-4,4-dimethyloxazolidines (**3**) and their evaluation in the laboratory as mosquito repellents.

Using high resolution NMR spectroscopy, we have shown[1–4] that *N*-acetyloxazolidines with alkyl (or alkenyl) groups at C-2 exist in solution as binary mixtures of rotational isomers (Fig. 2). The *Z* rotational isomer was found in excess over the *E* isomer. Thus, samples of **1** existed in chloroform solution mostly as the *Z* isomer (60–70% *Z*).

The promising mosquito repellent activity of *N*-acetyl-2-hexyloxazolidine (**1g**), *N*-acetyl-2-heptyloxazolidine (**1h**), *N*-acetyl-2-octyloxazolidine (**1i**) and *N*-acetyl-2-nonyloxazolidine (**1j**) prompted us to search for analogues of **1** of similar relative molecular mass that were enriched in the *Z* or *E* rotational isomer. We rationalized that comparative testing data on enriched samples of similar volatility and relative molecular mass (199–241) might indicate which rotational isomer was more

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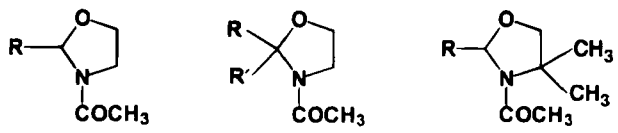
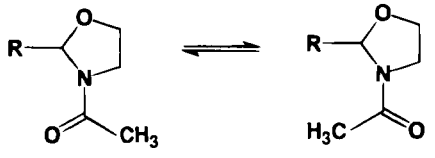


1 2 3

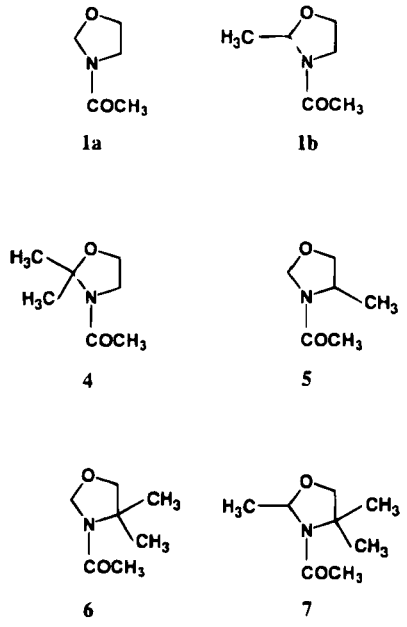
	R	R	R′	R
a	H	CH_3	$(CH_2)_2CH_3$	CH_2CH_3
b	CH_3	CH_3	$(CH_2)_4CH_3$	$(CH_2)_3CH_3$
c	CH_2CH_3	CH_3	$(CH_2)_5CH_3$	$(CH_2)_4CH_3$
d	$(CH_2)_2CH_3$	CH_2CH_3	$(CH_2)_4CH_3$	$(CH_2)_5CH_3$
e	$(CH_2)_3CH_3$	CH_3	$(CH_2)_6CH_3$	$(CH_2)_6CH_3$
f	$(CH_2)_4CH_3$	CH_2CH_3	$(CH_2)_5CH_3$	$(CH_2)_7CH_3$
g	$(CH_2)_5CH_3$	$(CH_2)_3CH_3$	$(CH_2)_5CH_3$	$(CH_2)_8CH_3$
h	$(CH_2)_6CH_3$	CH_3	$(CH_2)_7CH_3$	$(CH_2)_9CH_3$
i	$(CH_2)_7CH_3$	CH_2CH_3	$(CH_2)_6CH_3$	$(CH_2)_{10}CH_3$
j	$(CH_2)_8CH_3$	CH_3	$(CH_2)_8CH_3$	
k	$(CH_2)_9CH_3$			
l	$(CH_2)_{10}CH_3$			
m	$(CH_2)_{11}CH_3$			
n	$(CH_2)_{12}CH_3$			

Fig. 1. Structures of the experimental *N*-acetyloxazolidines.



Z *E*

Fig. 2. Rotational isomers of *N*-acetyl-2-alkyloxazolidines.



1a **1b**

4 5

6 7

Fig. 3. Structures of compounds used as models in molecular mechanics calculations.

biologically active and thus lead to the discovery of effective new insect repellents.

To identify target structures that would meet the above criteria, molecular mechanics calculations were utilized to predict the relative steric energy of the *Z* and *E* isomers of model *N*-acetyloxazolidines with methyl groups at C-2 and C-4 (Fig. 3). The choice of which members of **2** and **3** to synthesize was based on molecular modelling studies with these simpler analogues and on the commercial availability of starting materials that would provide samples spanning a molecular mass range of <199 to >241.

We have previously shown[2] that steric energies derived from molecular mechanics calculations can reliably predict the equilibrium isomer populations of *N*-acetyloxazolidine (**1a**), *N*-acetyl-2-methyloxazolidine (**1b**), **1i** and *N*-acetyl-2,2-dimethyloxazolidine (**4**), which were determined in solution by high resolution [^{13}C]NMR spectroscopy. NMR and molecular mechanics techniques have previously been used to investigate the rotameric preferences of *N*-acryloyl-2,2-dialkyloxazolidines for use in asymmetric cycloaddition reactions.[5]

2 EXPERIMENTAL METHODS

2.1 Molecular mechanics

Steric energies of the *Z* and *E* rotational isomers of *N*-acetyl-4-methyloxazolidine (Fig. 3, **5**), *N*-acetyl-4,4-dimethyloxazolidine (**6**) and *N*-acetyl-4,4-dimethyl-2-methyloxazolidine (**7**) were obtained as previously reported[2] for **1a**, **1b** and **4** using the MMX force field[6] of PCMODEL (ver. 3.2, Serena Software, Bloomington, IN). The starting geometry of the oxazolidine ring was flat. Separate energy minimizations were performed with torsional angles of 0° and 180° for the C-C-N-C atoms of the acetamide group and C-2 or C-4. The conformation of the energy-minimized structures resembled a C-5 envelope.[2]

2.2 General chemistry

Boiling points were recorded during distillations under reduced pressure and are uncorrected. Microanalyses were obtained from Galbraith Laboratories Inc. (Knoxville, TN) and from Guelph Chemical Laboratories Ltd (Guelph, Ontario) and were within $\pm 0.4\%$ of theory for C, H and N. Column chromatography was performed with Mallinckrodt CC-7 silica gel and hexane + diethyl ether. Purity was assessed by GC with a Hewlett-Packard model 5838A instrument equipped with a flame ionization detector and a 30-m column of DB-5 or DB-1. Mass spectra were recorded under electron-impact (70 eV) and chemical ionization (isobutane) conditions, using a Hewlett-Packard model

5985B GC/MS and a 30-m column of DB-5MS or SPB-1. Infrared spectra were obtained on a Perkin-Elmer model 137 instrument. Proton-decoupled [^{13}C]NMR spectra were acquired at 25°C in deuterochloroform solution (tetramethylsilane as internal reference) using a Bruker AM400 spectrometer.

The electron-impact mass spectral data and [^{13}C]NMR spectral assignments for **2a–2j** and **3a–3i** are reported in the Appendix (Tables A1–A4).

2.3 *N*-Acetyl-2,2-dialkyloxazolidines (Fig. 1, 2a–2j)

These compounds were prepared from ethanolamine (88 mmol) and the appropriate ketone (40 mmol, purchased from Aldrich or Eastman Kodak) in sodium-dried toluene (60 ml) by refluxing (5 h) with a Dean-Stark trap.[7] After removal of the water, acetic anhydride (88 mmol) was added to the ice-cold mixture and stirring was continued for 16–18 h. Workup involved washing with water, saturated sodium hydrogen carbonate and sodium chloride solutions. The organic phase was dried (magnesium sulfate) and the solvent was removed on a rotary evaporator (water aspirator vacuum). Pure samples were obtained by vacuum distillation with a fractionating column or by column chromatography followed by vacuum distillation.

2.4 *N*-Acetyl-2-alkyl-4,4-dimethyloxazolidines (Fig. 1, 3a–3i)

These compounds were prepared from 2-amino-2-methyl-1-propanol (Sigma) and the appropriate aldehyde (Aldrich) by the procedure described for compound **2**. Crude samples were purified by column chromatography followed by bulb-to-bulb vacuum distillation with a Büchi GKR-50 glass tube oven.

2.5 Biological testing

Mosquito repellent activity of the experimental chemicals was assessed in patch tests, a cloth system described previously.[1,3,8] Briefly, repellency using a human forearm as bait was determined by treating a muslin cloth with a test chemical (1 mg cm^{-2}) and exposing the cloth-covered skin of a volunteer's arm to approximately 1500 mosquitoes. Laboratory-reared *Aedes aegypti* (L.), *Anopheles quadrimaculatus* Say and *Anopheles albimanus* Wiedemann were used.

If more than three bites through the treated cloth occurred in 1 min, the chemical was classified as inactive. If zero to three bites were observed, the treated cloth was stored at room temperature (*c.*25°C) and retested at 24-h intervals thereafter until more than three bites per minute were recorded. *N*,*N*-Diethyl-*m*-toluamide (deet insect repellent) was used as a standard.

The minimum effective dosage (MED) for each experimental chemical and the standard was also determined,[1,3,8] at 15 min and at 24 h post-treatment. This bioassay was the same, except that the rate of treatment was reduced by one-half until more than three bites per minute were received at the lowest dose. Duration of repellency and MED values for **2a–2j** and **3a–3i** are tabulated in the Appendix (Table A5).

3 RESULTS AND DISCUSSION

3.1 Modelling

Molecular mechanics calculations with monomethyl derivatives showed that the *Z* rotational isomer was more stable with a methyl group at C-2 whereas the *E* isomer was preferred with a methyl group at C-4 (Table

TABLE 1
Relative Steric Energies from Molecular Mechanics Calculations and Equilibrium Isomer Populations of Model *N*-Acetyloxazolidines

	Z-Isomer		*E-Isomer*	
Compound[a]	*Relative energy* (*Kcal mol*$^{-1}$)	*Population*[b] (%)	*Relative energy* (*Kcal mol*$^{-1}$)	*Population*[b] (%)
1a	0	65·1	0·37	34·9
1b	0	88·5	1·21	11·5
4	0	98·6	2·53	1·4
5	0·33	36·4	0	63·6
6	1·65	5·8	0	94·2
7	0·65	25·0	0	75·0

[a] See Fig. 3.
[b] Calculated by ln(*E*-isomer population/*Z*-isomer population) = $-E/RT$ where the sum of the populations = 1 and T = 298 K (see Ref. 2).

1). With dimethyl derivatives, samples highly enriched in the *Z* isomer would be accessible with 2,2-dimethyl substitutions, whereas samples enriched in the *E* isomer would be obtained with 4,4-dimethyl groups. The trisubstituted oxazolidine (**7**) represented an interesting model because the *E* isomer was projected to be more stable than the *Z* isomer. This meant that the 2-methyl group could be replaced by a longer-chain alkyl group to obtain samples of molecular mass comparable to the most active members of **1**, yet displaying an equilibrium population favouring the *E* rather than the *Z* isomer.

3.2 Synthesis and spectroscopy

The potential *Z*-enriched samples **2a–2j** were isolated as clear liquids in moderate yields (29–72%) and characterized by NMR spectroscopy and mass spectrometry (Table 2).

The potential *E*-enriched samples **3a–3i** were also isolated as clear liquids (22–61% yield) and characterized by spectral techniques (Table 3).

Purified samples of **2** and **3** showed the expected amide carbonyl absorption (1640–1660 cm^{-1}) in their infrared spectra. Strong quasimolecular ions (M + 1) were observed in their chemical ionization mass spectra. The samples had a faint terpene-like odour or were odourless.

Previous NMR studies on **1a**, which was found to exist in deuterochloroform solution as a 60*Z*/40*E* mixture,[2] established that the [^{13}C] chemical shifts of C-2, C-4 and C-5 of the major (*Z*) isomer are downfield from the corresponding carbon signals of the minor (*E*) isomer. The [^{13}C]NMR spectra of **2a–2j** showed paired signals for these carbon atoms, with the major signal of each pair resonating downfield compared to the minor signal. This provided evidence that the major rotational isomer of these samples had the *Z* stereochemistry. Furthermore, the major rotational isomer of **4** previously

TABLE 2
Properties of Synthesized *N*-Acetyl-2,2-dialkyloxazolidines

Compound	*Formula*	*b.p.(°C) (mm Hg)*	*Yield (%)*	*Rotational isomer ratio*		*Relative molecular mass*
				Z	*E*	
2a	$C_9H_{17}NO_2$	67—73 (0·3)	29	95	5	171
2b	$C_{11}H_{21}NO_2$	89—91 (0·3)	52	96	4	199
2c	$C_{12}H_{23}NO_2$	84—86 (0·07)	69	95	5	213
2d	$C_{12}H_{23}NO_2$	79—81 (0·06)	70	93	7	213
2e	$C_{13}H_{25}NO_2$	82—87 (0·04)	57	95	5	227
2f	$C_{13}H_{25}NO_2$	81—82 (0·04)	66	94	6	227
2g	$C_{13}H_{25}NO_2$	82—84 (0·03)	62	95	5	227
2h	$C_{14}H_{27}NO_2$	92—94 (0·02)	63	95	5	241
2i	$C_{14}H_{27}NO_2$	98—101 (0·03)	72	91	9	241
2j	$C_{15}H_{29}NO_2$	117 (0·025)	40	95	5	255

TABLE 3
Properties of Synthesized *N*-Acetyl-2-alkyl-4,4-dimethyloxazolidines

Compound	*Formula*	*b.p.(°C) (mm Hg)*	*Yield (%)*	*Rotational isomer ratio*		*Relative molecular mass*
				Z	*E*	
3a	$C_9H_{17}NO_2$	94 (0·25)	22	31	69	171
3b	$C_{11}H_{21}NO_2$	113 (0·02)	49	29	71	199
3c	$C_{12}H_{23}NO_2$	97 (0·02)	61	34	66	213
3d	$C_{13}H_{25}NO_2$	88 (0·07)	57	32	68	227
3e	$C_{14}H_{27}NO_2$	116 (0·02)	54	33	67	241
3f	$C_{15}H_{29}NO_2$	127 (0·03)	45	31	69	255
3g	$C_{16}H_{31}NO_2$	125 (0·02)	28	33	67	269
3h	$C_{17}H_{33}NO_2$	136 (0·02)	51	32	68	283
3i	$C_{18}H_{35}NO_2$	157 (0·02)	30	30	70	297

has been shown by [^{1}H]NMR spectroscopy (NOESY experiments) to possess the *Z* stereochemistry.[2]

By comparing the peak heights of the paired signals of the ring carbons, **2a–2j** were found to be highly enriched in the *Z* isomer (91–96% *Z*).

Equilibrium isomer populations and *Z*/*E* stereochemical assignments for **3a–3i** were also determined by [^{13}C]NMR spectroscopy. Based on [^{13}C] chemical shifts of the paired signals for C-2 and C-5, the main component in the mixture was the *E* isomer (67–71% *E*) because the main signals were upfield compared to signals of the minor isomer. Curiously, the main signal of the quaternary carbon at C-4 resonated downfield relative to the minor signal.

These equilibrium populations found in deuterochloroform solution were in good agreement with the calculated (gas phase) equilibrium populations of model structures **4** and **7** (Table 1).

3.3 Structure–repellency relationships

The duration of effective repellency in the patch tests was used to compare the activity of the three series of homologous *N*-acetyloxazolidines against the three species of mosquitoes. As previously reported,[1] **1a–1n** showed the best repellency against *Ae. aegypti* and *An. quadrimaculatus*, with test samples falling in the relative molecular mass range of 199–255 (**1g–1k**). Repellency to *An. albimanus* required a narrower range of 199–227 (**1g–1i**).

Plots of duration of repellency versus molecular mass (Fig. 4) showed a similar trend against these species but **2a–2j** and **3a–3i** did not protect from mosquito bites for as long as samples of **1**. Samples of **2** and **3** were practically inactive against *An. albimanus*.

In a review on the design of insect repellents,[9] the authors concluded that topical mosquito repellents fall in a molecular mass range of approximately 150–250. This range is corroborated in the present study. Recently described neoalkanamides also fell into a similar range (185–227) for effective cockroach repellent activity.[10]

Within the 2,2-dialkyl series, chemicals with the same molecular mass (**2c** and **2d**; **2e**, **2f** and **2g**; **2h** and **2i**) displayed quite different activity against *Ae. aegypti*. The most active compounds (**2c**, **2e** and **2h**) had a methyl group as the R′ substituent. This structural requirement was not apparent against *An. quadrimaculatus* because samples of **2** of the same molecular mass displayed essentially the same mosquito repellent activity.

N-Acetyloxazolidines of relative molecular mass 227 showed the best activity against *Ae. aegypti*. Figure 5 represents a graph of repellency versus *Z*/*E* ratios for the experimental chemicals of this molecular mass. A

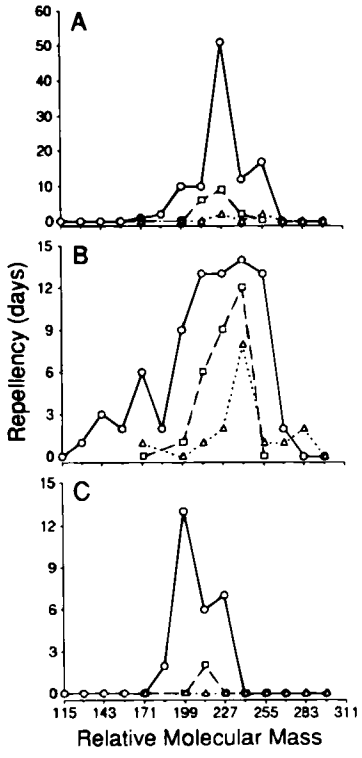


Fig. 4. Effect of relative molecular mass on duration of repellency in mosquito bioassays with (A) *Ae. aegypti*, (B) *An. quadrimaculatus* and (C) *An. albimanus*. (○———○) **1** (**1a–1n**), (□- - - -□) **2** (**2a, 2b, 2c, 2e, 2h, 2j**), (△- - -△) **3** (**3a–3i**).

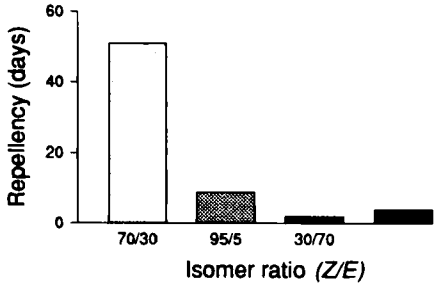


Fig. 5. Comparison of mosquito repellency (*Ae. aegypti*) of experimental chemicals with the same relative molecular mass (227) but with different equilibrium populations of rotational isomers. (▨) **1i**, (▩) **2e**, (▨) **3d**, (■) deet.

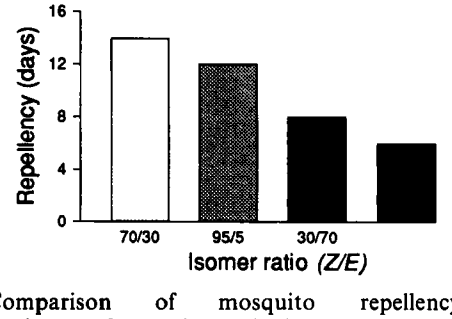


Fig. 6. Comparison of mosquito repellency (*An. quadrimaculatus*) of experimental chemicals with the same relative molecular mass (241) but with different equilibrium populations of rotational isomers. (▨) **1j**, (▩) **2h**, (▨) **3e**, (■) deet.

graph is also shown for oxazolidines of relative molecular mass 241 against *An. quadrimaculatus* (Fig. 6).

Differences in the bioactivity of rotational isomers of heterocyclic amides have been indicated in the literature.[11,12] These differences have been rationalized by the conformational preferences of one isomer, resulting in a better fit to the target enzyme or receptor. Among the *N*-acetyloxazolidines discussed here, samples partially enriched in the *Z* isomer showed the best mosquito repellency. Thus, the 70*Z*/30*E* mixture of **1i** was more effective against *Ae. aegypti* than the 95*Z*/5*E* mixture of **2e** or the 30*Z*/70*E* mixture of **3d.** Against *An. quadrimaculatus*, the trends were similar (**1j** > **2h** > **3e**) but differences in repellency were not as pronounced.

Among these highly flexible *N*-acetyloxazolidines, the population of rotational isomers was modulated by structural changes, which also affect bioactivity. It is therefore difficult to prove that a specific *Z*/*E* ratio is important. Conformationally rigid amides such as cyclic lactams might provide additional insight if optimal volatility, an important consideration in designing topical inset repellents,[9] can be retained.

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APPENDIX: SUPPLEMENTARY DATA

TABLE A1
Electron-Impact (70 eV) Mass Spectral Data from GC/MS Analyses of **2a–2j**
m/z (relative intensity)

Compound number	$M^{+\cdot}$	*Fragment ions of ≧ 10% relative intensity*
2a	171 (0)	128 (59), 141 (30), 86 (100), 56 (10), 44 (38), 43 (59), 42 (18), 41 (15)
2b	199 (0)	142 (24), 128 (74), 86 (100), 55 (10), 44 (30), 43 (49), 42 (12), 41 (12)
2c	213 (0)	156 (18), 128 (100), 86 (86), 43 (10)
2d	213 (0)	184 (16), 142 (100), 100 (43), 44 (11)
2e	227 (0)	170 (17), 128 (100), 86 (85)
2f	227 (0)	198 (28), 156 (100), 142 (82), 100 (65)
2g	227 (0)	170 (65), 128 (100), 44 (10)
2h	241 (0)	184 (11), 128 (100), 86 (73)
2i	241 (0)	212 (21), 170 (80), 142 (94), 100 (100), 98 (11), 86 (10), 57 (10), 44 (16), 43 (19)
2j	255 (0)	198 (20), 128 (100), 86 (72), 44 (20), 43 (40), 41 (18)

TABLE A2
Electron-Impact (70 eV) Mass Spectral Data from GC/MS Analyses of **3a–3i**
m/z (relative intensity)

Compound number	$M^{+\cdot}$	*Fragment ions of ≧ 10% relative intensity*
3a	171 (0)	142 (34), 100 (100), 55 (13), 43 (19), 42 (11)
3b	199 (0)	142 (51), 100 (100), 55 (14), 43 (25), 42 (12), 41 (10)
3c	213 (0)	142 (58), 100 (100), 55 (15), 43 (27), 42 (11), 41 (11)
3d	227 (0)	142 (49), 100 (100), 55 (10), 43 (23), 41 (12)
3e	241 (0)	142 (57), 100 (100), 55 (15), 43 (25), 41 (14)
3f	255 (0)	142 (65), 100 (100), 55 (15), 43 (20), 41 (14)
3g	269 (0)	142 (78), 100 (100), 55 (11), 43 (23), 41 (12)
3h	283 (0)	142 (78), 100 (100), 55 (22), 43 (37), 41 (18)
3i	297 (0)	142 (64), 100 (100), 55 (16), 43 (24), 41 (14)

TABLE A3
Carbon-13 NMR Chemical Shifts of **2a–2j** in deuterochloroform at 25°C[a]

Compound number	*Stereochemistry*	*Composition of mixture (%)*	*C = 0*	*C-2*	*C-4*	*C-5*	*Other signals*[b]
2a	*Z*	95	167·04	96·62	47·59	63·15	14·04—41·58 (9)
	E	5	167·04	94·44	46·90	62·26	
2b	*Z*	96	166·96	96·60	47·59	63·15	14·04—39·37 (14)
	E	4	166·96	94·47	46·91	62·24	
2c	*Z*	95	166·98	96·72	47·62	63·17	14·07 39·50 (13)
	E	5	166·98	94·52	46·94	62·31	
2d	*Z*	93	166·99	99·38	48·14	63·88	7·61 —38·13 (14)
	E	7	167·24	97·09	47·46	62·95	
2e	*Z*	95	167·02	96·65	47·59	63·15	14·12 39·41 (15)
	E	5	167·02	94·50	46·93	62·26	
2f	*Z*	94	166·99	99·40	48·15	63·89	7·64 —38·19 (16)
	E	6	167·24	97·12	47·48	62·98	
2g	*Z*	95	166·96	99·05	48·03	63·81	14·03—38·22 (9)
	E	5	167·21	96·84	47·40	62·91	
2h	*Z*	95	166·98	96·65	47·57	63·12	14·09—39·40 (41)
	E	5	166·98	94·50	46·90	62·25	
2i	*Z*	91	167·01	99·41	48·15	63·89	7·64 38·21 (22)
	E	9	167·26	97·12	47·49	62·98	
2j	*Z*	95	166·66	96·31	47·32	62·87	13·84—39·15 (14)
	E	5	166·66	94·19	46·65	61·96	

[a] In ppm from internal TMS. Precision ± 0.02 ppm.
[b] These are overlapping signals from methyl carbons attached to positions 2 and 3 as well as from methylene carbons of alkyl groups. The number of signals observed in this region is shown in brackets.

TABLE A4
Carbon-13 NMR Chemical Shifts of **3a–3i** in deuterochloroform at 25°C[a]

Compound number	*Stereochemistry*	*Composition of mixture (%)*	*C = 0*	*C-2*	*C-4*	*C-5*	*Other signals*[b]	CH_3 [c]
3a	*Z*	31	168·13	93·42	58·27	78·79	23·5— 27·38 (8)	8·88
	E	69	166·74	92·26	60·25	77·79		9·27
3b	*Z*	29	168·03	92·58	58·19	78·87	22·29 34·02 (12)	10·09
	E	71	166·62	91·19	60·19	77·81		10·09
3c	*Z*	34	168·04	92·59	58·21	78·81	22·61 34·27 (12)	13·96
	E	66	166·65	91·19	60·19	77·81		13·96
3d	*Z*	32	168·04	92·62	58·21	78·83	22·56— 34·33 (14)	14·07
	E	68	166·63	91·22	60·21	77·84		14·07
3e	*Z*	33	168·04	92·60	58·21	78·81	22·62 34·31 (16)	14·09
	E	67	166·63	91·20	60·19	77·82		14·09
3f	*Z*	31	168·04	92·65	58·22	78·86	22·67— 34·38 (14)	14·09
	E	69	166·64	91·24	60·23	77·87		14·09
3g	*Z*	33	168·04	92·62	58·21	78·81	22·67 34·32 (16)	14·12
	E	67	166·65	91·21	60·20	77·82		14·12
3h	*Z*	32	168·04	92·61	58·21	78·81	22·69— 34·31 (16)	14·12
	E	68	166·65	91·12	60·20	77·82		14·12
3i	*Z*	30	168·03	92·60	58·20	78·81	22·69— 34·31 (17)	14·12
	E	70	166·63	91·20	60·19	77·81		14·12

[a] In ppm from internal TMS. Precision ± 0.02 ppm.
[b] These overlapping signals originate from methyl carbons at N-3 and C-4 as well as from the methylene carbons of alkyl groups. The number of signals observed in this region is shown in brackets.
[c] Signals from the methyl carbon of the alkyl group at C-2.

TABLE A5
Mosquito Repellency Data for **2a–2j** and **3a–3i** in Patch Tests

	Number of days effective			*Minimum effective dose (mg cm^{-2})*					
	At 1.0 mg cm^{-2}			*At 15 min*			*At 24 h*		
Compound	*Ae. aeg.*	*An. quad.*	*An. alb.*	*Ae. aeg.*	*An. quad.*	*An. alb.*	*Ae. aeg.*	*An. quad.*	*An. alb.*
2a	0[a]	0[a]	0[a]	0·125	0·063	0·25	>1	>1	>1
2b	0[a]	1	0[a]	0·125	0·032	0·125	>1	1	>1
2c	6	6	2	0·032	0·004	0·125	1	0·5	1
2d	1	6	1	0·032	0·002	0·5	1	0·5	1
2e	9	9	0	0·063	0·004	>1	0·25	0·25	
2f	7	8	0[a]	0·016	0·002	1	0·5	0·5	>1
2g	1	8	0	0·063	0·002	>1	0·5	0·5	
2h	2	12	0	0·25	0·008	>1	0·25	0·125	
2i	0	12	0	>1	0·008	>1		0·125	
2j	0[a]	0[a]	0	0·032	0·016	>1	>1	>1	
3a	0[a]	1	0[a]	0·25	0·063	0·5	>1	1	>1
3b	0[a]	0[a]	0[a]	0·125	0·063	0·125	>1	>1	>1
3c	0[a]	1	0[a]	0·25	0·063	0·5	>1	1	>1
3d	2	2	0[a]	0·125	0·032	0·25	0·5	0·5	>1
3e	0	8	0	>1	0·032	>1		0·5	
3f	2	1	0	0·063	0·016	>1	1	1	
3g	0	1	0	>1	0·25	>1		1	
3h	0	2	0	>1	0·25	>1		1	
3i	0	0	0	>1	1	>1		>1	
Deet[b]	4·2 (±2·2)	5·2 (±1·7)	2·2 (±0·5)	0·032 (±0·0)	0·015 (±0·012)	0·18 (±0·22)	0·328 (±0·212)	0·172 (±0·094)	0·687 (±0·375)

[a] These compounds demonstrated repellency at 15 min post-treatment but were ineffective at 24 h post-treatment.
[b] Repellency data for this standard are expressed as the mean (±S.D.) of four separate tests.

REFERENCES

1. Taylor, W. G. & Schreck, C. E., Synthesis and mosquito repellent properties of some 2-alkyl-*N*-acetyloxazolidines. *Pestic. Sci.*, **33** (1991) 1–9.
2. Taylor, W. G., Hall, T. W. & Schreck, C. E., An investigation of the rotational isomers of *N*-acetyl-2,2-dimethyloxazolidine and related compounds by nuclear magnetic resonance spectroscopy and molecular mechanics. *Can. J. Chem.*, **70** (1992) 165–172.
3. Taylor, W. G. & Schreck, C. E., Nuclear magnetic resonance spectra and mosquito repellent properties of some oxazolidine derivatives of 5-methyl-4-hexenal. *J. Pharm. Sci.*, **78** (1989) 109–113.
4. Taylor, W. G. & Nakashima, T. T., Diastereomers of the insect repellent 3-acetyl-2-(2′,6′-dimethyl-5′-heptenyl)oxazolidine. Isolation by high pressure liquid chromatography and characterization by ^{13}C nuclear magnetic resonance spectroscopy. *Can. J. Chem.*, **62** (1984) 96–100.
5. Kanemasa, S. & Onimura, K., New chiral auxiliaries based on conformational control, a C_2-symmetric 2,2-dimethylimidazolidine and 4-chiral 2,2-dialkyloxazolidines. Synthesis and conformational analysis of acrylamide derivatives. *Tetrahedron*, **48** (1992) 8631–8644.
6. Gajewski, J. J., Gilbert, K. E. & McKelvey, J., MMX an enhanced version of MM2. In *Advances in Molecular Modeling, Vol. 2*, ed. D. Liotta. JAI Press, Greenwich, Connecticut, 1990, pp. 65–92.
7. Taylor, W. G., Diastereomers of the insect repellent 3-acetyl-2-(2,6-dimethyl-5-heptenyl) oxazolidine: Evidence from glass capillary gas chromatography and mass spectrometry. *J. Agric. Food Chem.*, **30** (1982) 409–411.
8. Taylor, W. G. & Schreck, C. E., Chiral-phase capillary gas chromatography and mosquito repellent activity of some oxazolidine derivatives of (+)- and (−)-citronellal. *J. Pharm. Sci.*, **74** (1985) 534–539.
9. Skinner, W. A. & Johnson, H. L., The design of insect repellents. In *Drug Design, Vol. 10*, ed. E. J. Ariens. Academic Press, New York, 1980, pp. 277–305.
10. Steltenkamp, R. J., Hamilton, R. L., Cooper, R. A. & Schal, C., Alkyl and aryl neoalkanamides: Highly effective insect repellents. *J. Med. Entomol.*, **29** (1992) 141–149.
11. Bennion, C., Brown, R. C., Cook, A. R., Manners, C. N., Payling, D. W. & Robinson, D. H., Design, synthesis and physicochemical properties of a novel, conformationally restricted 2,3-dihydro-1,3,4-thiazole-containing angiotensin converting enzyme inhibitor which is preferentially eliminated by the biliary route in rats. *J. Med. Chem.*, **34** (1991) 439–447.
12. Amodeo, P., Morelli, M. A. C. & Motta, A., Multiple conformations and proline cis-trans isomerization in salmon calcitonin: A combined nuclear magnetic resonance, distance geometry and molecular mechanics study. *Biochemistry*, **33** (1994) 10754–10762.